Personalized medicine in cerebrovascular neurosurgery: precision neurosurgical ma...

Health & Medicine

Introduction

Cerebral aneurysms are common vascular lesions with prevalence in autopsy studies as high as 5% (1). The most common clinical presentation of cerebral aneurysms is rupture leading to subarachnoid hemorrhage (SAH) (2). The estimated incidence of SAH from ruptured intracranial aneurysms in the United States is one case per 10, 000 persons (2 , 3). An estimated 10% of these patients die before reaching medical attention with the 30-day mortality rate reaching as high as 45%. The 30% of patients who do survive suffer significant disability (3 – 5).

Aneurysms that present with SAH represent unstable lesions with significant risk of re-rupture, with recurrent hemorrhage within the first 24 h in as many as 4%, and in as many as 20% within the first 2 weeks of the initial event, if left unsecure (2). Symptomatic unruptured aneurysms presenting with new cranial nerve palsies or brainstem dysfunction are at increased risk of rupture, as high as 6% per year, and should be treated (6).

Recent advances in genomic and proteomic technologies have enabled the identification of molecular characteristics that may prove useful in tracking aneurysm growth and progression to guide treatment of unruptured aneurysms. Novel quantitative neuroimaging technologies have also recently emerged, capable of non-invasive characterization of hemodynamic factors, inflammation, and structural changes in aneurysmal walls. The combined use of these quantitative neuroimaging and molecular-based approaches, called

Radiogenomics , is a technique that holds great promise in better characterizing individual aneurysms.

Beyond securing the aneurysm from risk of rupture, the treatment of patients with aneurysmal SAH includes managing a significant spectrum of secondary sequelae, which can include cerebral vasospasm (CV), delayed ischemia, seizures, cerebral edema, hydrocephalus, and endocrinologic and catecholamine-induced systemic dysfunction in cardiac, pulmonary, and renal systems. Optimizing management of these complex multisystem factors is critical for improving the 30-day mortality rate (as high as 45%) and the proportion of significantly disabled survivors (as high as 30%). An increased focus on understanding the pathophysiology and molecular characteristics of these secondary processes will enable the development of targeted therapeutics and novel diagnostics for improved patient selection in personalized medicine trials for SAH.

Current Controversies in the Management of Cerebral Aneurysms

The management of asymptomatic unruptured aneurysms is the subject of ongoing controversy. A recent prospective observational cohort study, The International Study of Unruptured Intracranial Aneurysms (ISUIA), in which 1, 692 patients were preselected to be conservatively followed, reported that the subgroup with the smallest aneurysms (defined in this study as <7 mm) had an observed 5-year rupture rate of 0% during the interval they were followed (1). Controversy surrounding the methodology of this study exists because, unlike a true natural history study, patients may have been

preselected for inclusion on the basis of their surgeons' opinions that these aneurysms were less likely to rupture. Consistent with this, the rupture rates of this observational cohort were significantly lower than in other studies of unruptured cerebral aneurysms (2 , 7 – 10). Another controversy was the ISUIA-reported risk of morbidity associated with microsurgical clipping of unruptured aneurysms as 15. 7% after 1 year, which raised significant concerns when compared to the literature reporting surgical morbidity in the range of 3–7% (2). The result of inappropriately generalizing the ISUIA data of a preselected subset of aneurysms has nonetheless had the important effect of at least temporarily discouraging the treatment of many unruptured cerebral aneurysms. The result this will have on actual patient outcomes in real-world populations remains to be seen. In the interim, it is vitally important to generate improved biomarkers that move past arbitrary size cutoffs so that clinicians can better characterize rupture risk in individual lesions and thus improve decision-making for each unique patient.

Moving beyond the question of when to intervene, the issue of how to intervene is also the subject of much controversy, with options including microsurgical clipping and endovascular coiling. The International Subarachnoid Aneurysm Trial (ISAT) reported prospectively randomizing 2, 143 patients, who presented with ruptured aneurysms, to either clipping or coiling (11). an important caveat of this analysis is that these 2, 143 patients represented only a fraction of the total 9, 559 patients the study initially assessed with aneurysmal SAH. The vast majority of real-world aneurysmal SAH patients (77. 6%) were excluded upfront from this analysis,

based on inclusion criteria that resulted in an analysis of a minority of aneurysmal SAH patients. The clinical characteristics of the resulting study demonstrated the profound effects of this selection bias, including 90% having favorable clinical grade, 95% having aneurysms in the anterior circulation, and 90% of aneurysms being <10 mm. Generalizing these findings may be inappropriate, and in fact many contributors to the ISAT trial have themselves pointed out significant issues with data transparency and need for secondary sources of data on this critical topic (12). As a result of these significant limitations of ISUIA and ISAT, and despite the impact they have already had on current treatments, whether to observe, surgically treat, or endovascularly manage intracranial aneurysms remains controversial.

Whether the increased durability of clipping outweighs its slightly higher risks compared to coiling is unknown. In fact, even ISAT investigators reported that the rehemorrhage rates and recoiling rates in subsequent analyses of their data indicate significant problems with the study's original conclusions (12). Nevertheless, endovascular technology is likely to continue to advance with indications and outcomes likely to be constantly changing.

As such, patient-specific biomarkers that better predict which aneurysms represent high-risk lesions and which lesions are likely to respond best to a particular therapy are of vital importance.

Emerging Biomarkers in the Management of Unruptured Cerebral Aneurysms

Although the pathogenesis of cerebral aneurysms is unknown, their development at stereotyped locations associated with specific hemodynamic factors suggests that regional blood flow patterns play a fundamental role in the pathophysiology of the disease (13 – 16), as recently reviewed by Can and Du (17). Using non-invasive quantitative imaging to characterize aneurysm morphology and computational fluid dynamics analyses of resulting hemodynamics, these studies have provided new insight into the key factors that play in a role in aneurysm progression and risk of rupture. Interestingly, bifurcation aneurysms were associated with high wall shear stress (WSS), suggesting that wall remodeling and degeneration *via* endothelial injury is of greatest relevance in these aneurysms. In contrast, sidewall aneurysms were associated with low WSS, suggesting that stasis of blood flow, and resulting endothelial dysfunction with pro-inflammatory-mediated degeneration of the aneurysm wall, may be more clinically relevant in these aneurysms (17). In paired analysis of unruptured aneurysms that went on to rupture, the hemodynamic factors associated with rupture risk included low shear index area (LSA), defined as the area of the aneurysm wall exposed to a WSS <10% of the mean parent vessel, which was observed to be higher in aneurysms that went on to rupture (i. e., a greater percentage of the aneurysm wall was exposed to low shear stresses). However, patients with ruptured aneurysms experienced a higher maximum WSS (17). Taken together, these data suggest that a significant area of low shear stress results in endothelial dysfunction and degeneration

of the aneurysmal wall to the point of susceptibility, and that focally high WSS exerted against this background results in the subsequent rupture event. These hemodynamic parameters of LSA and WSS provide a more dynamic measure of the aneurysm than arbitrary size measurement cutoffs proposed by the ISUIA and ISAT studies, and these next generation parameters will likely play an increasing role in the patient-specific characterization of aneurysms and associated clinical decision-making in the future.

Recently, ferumoxytol-enhanced magnetic resonance imaging has shown promise in non-invasively characterizing aneurysm inflammation. Increased ferumoxytol uptake in aneurysm walls is a measure of myeloid cell inflammation, and has predicted aneurysm instability and an increased 6-month rupture risk in pilot studies. Thus, increased ferumoxytol uptake may serve as a biomarker for lesions warranting urgent intervention (18 – 20). As hemodynamic factors, such as high LSA, may result in a pro-inflammatory milieu, with subsequent endothelial apoptosis and aneurysmal wall degeneration (17), a combination of hemodynamic and inflammatory characterization by newer non-invasive neuroimaging modalities may become increasingly important in the patient-specific management of aneurysms in the near future.

Emerging Biomarkers in the Management of Secondary Sequelae of SAH

Secondary sequelae of SAH include CV, delayed ischemia, seizures, cerebral edema, hydrocephalus, and endocrinologic and catecholamine-induced

systemic dysfunction in cardiac, pulmonary, and renal systems. Currently there are no established biomarkers for preclinical diagnosis or monitoring of progression of these secondary sequelae.

Hydrocephalus can develop in up to 20% of patients who have aneurysmal SAH (2), requiring ventriculostomy for drainage of cerebrospinal fluid (CSF). There are currently no accurate predictors of shunt dependency after ventriculostomy placement in SAH, but emerging CSF-based biomarkers that reflect the rate of CSF clearance, as well as neuroimaging that quantifies CSF dynamics, hold promise in selecting patients for rapid removal of the external ventricular drain to minimize risks of ventriculitis.

Cerebral vasospasm is a major cause of morbidity and mortality in SAH and refers to intracranial vasoconstriction that may occur between 3 and 14 days after SAH. The pathogenesis of vasospasm is unknown and even with maximal therapy vasospasm can cause strokes and death (21). Approximately two-thirds of all patients with SAH who undergo cerebral angiography will demonstrate radiographic evidence of vasospasm, known as angiographic CV. Symptomatic (clinical) CV, defined as the development of new focal neurologic deficits in patients with SAH in association with angiographic CV and not attributable to other causes, occurs in approximately one-third of all patients with SAH. Approximately one-third of these patients with CV die from the CV-related infarcts and another one-third are left significantly disabled. Medical treatment of CV consists of orally administered nimodipine (60 mg every 4 h for 21 days), which has been shown to improve outcome after SAH (22). Patients are monitored with

daily transcranial Doppler (TCD) velocities, and in patients who develop elevated TCDs and new neurologic deficits, triple-H therapy is initiated (hypertension, hypervolemia, and hemodilution) (3). Patients with persisting neurologic deficit undergo urgent catheter angiography to confirm the presence of vasospasm and if confirmed are treated with intra-arterial administration of smooth muscle relaxants, such as papaverine or nicardipine or with balloon angioplasty. These antispasmodic therapies can result in angiographically confirmed arterial dilatation in > 90% of patients (23 – 25).

Multiple CSF biomarkers have been identified for the early diagnosis of symptomatic CV, as recently reviewed by Lad et al. (26), which may help guide patient-specific selection for personalized medicine trials aimed at preventing delayed ischemic neurologic deficits, such as protocols using earlier angiography for early intra-arterial smooth muscle relaxant therapy. Endothelin-1 has been shown to significantly increase days 4–7 after SAH in patients who develop symptomatic CV versus those who do not (27), and this increase predicts the occurrence of symptomatic CV (28). CSF interleukin (IL)-6 levels also significantly increase in the first 4–5 days after disease onset in patients with CV compared to those with uncomplicated SAH (29). These data suggest that endothelin-1 and IL-6 could be useful diagnostic and predictive markers for CV and potentially useful tools for personalized medicine protocols in the treatment and prevention of symptomatic CV.

Subarachnoid hemorrhage can result in overactivity of the sympathetic nervous system and catecholamine surge with resulting multisystem dysfunction. Cardiac abnormalities after SAH are common, including electrocardiographic changes, elevations in cardiac enzymes, and left ventricular dysfunction in up to one-third of cases (30 – 32). These abnormalities appear to directly result from the excessive catecholamine release in response to the intracranial hemorrhage (33). In some patients, other adverse events from this catecholamine surge include pulmonary edema, hypotension requiring vasopressors, delayed strokes, and death (34). The combination of decreased cardiac contractility, increased pulmonary vascular permeability, increased pulmonary vascular pressure, and increased volume from resuscitation results in the development of this pulmonary edema, and increased preload results in stretching of the cardiac atrium and atrial natriuretic peptide release (peaks on day 2) (35). This natriuretic peptide acts on renal tubules, triggering sodium and volume loss, and without appropriate resuscitation, plasma sodium levels fall significantly by post-rupture days 4–6, which can be preempted by judicious volume and salt replacement. This has been shown to reduce the incidence of severe CV (36). The relationship between natriuretic and diuretic states after aneurysmal SAH and the subsequent development of CV, particularly with regards to activation of the renin–angiotensin–aldosterone system between days 4 and 6, warrant further study and may provide further biomarkers to guide patient-specific treatments that optimize sodium and fluid balance, address natriuretic and renin–angiotensin–aldosterone signaling dysfunction, and

provide appropriate inotropic and vasopressor support during myocardial dysfunction and ventilator support during neurogenic pulmonary edema.

Conclusion

Patient-specific biomarkers that better predict which cerebral aneurysms represent high-risk lesions worthy of intervention are of vital importance. Personalized treatment strategies are also increasingly important in the management of secondary sequelae from SAH, including CV, delayed ischemia, seizures, cerebral edema, hydrocephalus, and endocrinologic and catecholamine-induced systemic dysfunction in cardiac, pulmonary, and renal systems. The combined use of these quantitative neuroimaging and molecular-based approaches, called *Radiogenomics* , is a technique that holds great promise in better characterizing individual aneurysms. In the near future, these radiogenomic techniques may help improve quality of life and patient outcomes *via* patient-specific approaches to the treatment of unruptured cerebral aneurysms and personalized medical management of secondary processes following aneurysmal SAH.

Author Contributions

All authors listed, have made substantial, direct and intellectual contribution to the work, and approved it for publication.

Conflict of Interest Statement

Dr. Steinberg is a consultant for Qool Therapeutics and for Peter Lazic US, Inc.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This work was supported in part with funding from William Randolph Hearst Foundation, Bernard and Ronni Lacroute, and Russell and Elizabeth Siegelman (GS).

References

1. Wiebers DO, Whisnant JP, Huston J III, Meissner I, Brown RD Jr, Piepgras DG, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and endovascular treatment. *Lancet* (2003) 362(9378): 103–10. doi: 10. 1016/S0140-6736(03)13860-3

PubMed Abstract | CrossRef Full Text | Google Scholar

2. Brisman JL, Song JK, Newell DW. Cerebral aneurysms. *N Engl J Med* (2006) 355(9): 928–39. doi: 10. 1056/NEJMra052760

CrossRef Full Text | Google Scholar

3. Wijdicks EF, Kallmes DF, Manno EM, Fulgham JR, Piepgras DG. Subarachnoid hemorrhage: neurointensive care and aneurysm repair. *Mayo Clin Proc* (2005) 80(4): 550–9. doi: 10. 1016/S0025-6196(11)63210-2

PubMed Abstract | CrossRef Full Text | Google Scholar

4. Bederson JB, Awad IA, Wiebers DO, Piepgras D, Haley EC Jr, Brott T, et al. Recommendations for the management of patients with unruptured intracranial aneurysms: a statement for healthcare professionals from the Stroke Council of the American Heart Association. *Stroke* (2000) 31(11): 2742–50. doi: 10. 1161/01. STR. 31. 11. 2742

CrossRef Full Text | Google Scholar

5. Johnston SC, Selvin S, Gress DR. The burden, trends, and demographics of mortality from subarachnoid hemorrhage. *Neurology* (1998) 50(5): 1413–8. doi: 10. 1212/WNL. 50. 5. 1413

PubMed Abstract | CrossRef Full Text | Google Scholar

6. Wiebers DO, Whisnant JP, Sundt TM Jr, O'Fallon WM. The significance of unruptured intracranial saccular aneurysms. *J Neurosurg* (1987) 66(1): 23–9. doi: 10. 3171/jns. 1987. 66. 1. 0023

PubMed Abstract | CrossRef Full Text | Google Scholar

7. Ausman JI. The New England Journal of Medicine report on unruptured intracranial aneurysms: a critique. *Surg Neurol* (1999) 51(2): 227–9.

Google Scholar

8. Juvela S, Porras M, Poussa K. Natural history of unruptured intracranial aneurysms: probability of and risk factors for aneurysm rupture. *J Neurosurg* (2000) 93(3): 379–87. doi: 10. 3171/jns. 2000. 93. 3. 0379

PubMed Abstract | CrossRef Full Text | Google Scholar

9. Kobayashi S, Orz Y, George B, Lee KC, Alexander MJ, Spetzler RF, et al. Treatment of unruptured cerebral aneurysms. *Surg Neurol* (1999) 51(4): 355–62.

Google Scholar

10. Tsutsumi K, Ueki K, Morita A, Kirino T. Risk of rupture from incidental cerebral aneurysms. *J Neurosurg* (2000) 93(4): 550–3. doi: 10. 3171/jns. 2000. 93. 4. 0550

PubMed Abstract | CrossRef Full Text | Google Scholar

11. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, et al. Aneurysm Trial Collaborative: international subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. *Lancet* (2005) 366(9488): 809–17. doi: 10. 1016/S0140-6736(05)67214-5

CrossRef Full Text | Google Scholar

12. Tait MJ, Critchley GR, Norris JS. How much can be concluded from the International Subarachnoid Aneurysm Trial (ISAT)? *Br J Neurosurg* (2007) 21(1): 3–6. doi: 10. 1080/02688690601170726

PubMed Abstract | CrossRef Full Text | Google Scholar

13. Cebral JR, Mut F, Weir J, Putman C. Quantitative characterization of the hemodynamic environment in ruptured and unruptured brain aneurysms. *AJNR Am J Neuroradiol* (2011) 32(1): 145–51. doi: 10. 3174/ajnr. A2419

PubMed Abstract | CrossRef Full Text | Google Scholar

14. Jou LD, Lee DH, Morsi H, Mawad ME. Wall shear stress on ruptured and unruptured intracranial aneurysms at the internal carotid artery. *AJNR Am J Neuroradiol* (2008) 29(9): 1761–7. doi: 10. 3174/ajnr. A1180

PubMed Abstract | CrossRef Full Text | Google Scholar

15. Shojima M, Oshima M, Takagi K, Torii R, Hayakawa M, Katada K, et al. Magnitude and role of wall shear stress on cerebral aneurysm: computational fluid dynamic study of 20 middle cerebral artery aneurysms. *Stroke* (2004) 35(11): 2500–5. doi: 10. 1161/01. STR. 0000144648. 89172. 0f

PubMed Abstract | CrossRef Full Text | Google Scholar

16. Xiang J, Natarajan SK, Tremmel M, Ma D, Mocco J, Hopkins LN, et al. Hemodynamic-morphologic discriminants for intracranial aneurysm rupture. *Stroke* (2011) 42(1): 144–52. doi: 10. 1161/STROKEAHA. 110. 592923

PubMed Abstract | CrossRef Full Text | Google Scholar

17. Can A, Du R. Association of hemodynamic factors with intracranial aneurysm formation and rupture: systematic review and meta-analysis. *Neurosurgery* (2016) 78(4): 510–20. doi: 10. 1227/NEU. 0000000000001083

PubMed Abstract | CrossRef Full Text | Google Scholar

18. Hasan D, Chalouhi N, Jabbour P, Dumont AS, Kung DK, Magnotta VA, et al. Early change in ferumoxytol-enhanced magnetic resonance imaging signal suggests unstable human cerebral aneurysm: a pilot study. *Stroke* (2012) 43(12): 3258–65. doi: 10. 1161/STROKEAHA. 112. 673400

PubMed Abstract | CrossRef Full Text | Google Scholar

19. Hasan DM, Mahaney KB, Magnotta VA, Kung DK, Lawton MT, Hashimoto T, et al. Macrophage imaging within human cerebral aneurysms wall using ferumoxytol-enhanced MRI: a pilot study. *Arterioscler Thromb Vasc Biol* (2012) 32(4): 1032–8. doi: 10. 1161/ATVBAHA. 111. 239871

PubMed Abstract | CrossRef Full Text | Google Scholar

20. Hasan DM, Chalouhi N, Jabbour P, Magnotta VA, Kung DK, Young WL. Imaging aspirin effect on macrophages in the wall of human cerebral aneurysms using ferumoxytol-enhanced MRI: preliminary results. *J Neuroradiol* (2013) 40(3): 187–91. doi: 10. 1016/j. neurad. 2012. 09. 002

PubMed Abstract | CrossRef Full Text | Google Scholar

21. Keyrouz SG, Diringer MN. Clinical review: prevention and therapy of vasospasm in subarachnoid hemorrhage. *Crit Care* (2007) 11(4): 220. doi: 10. 1186/cc5958

PubMed Abstract | CrossRef Full Text | Google Scholar

22. Barker FG II, Ogilvy CS. Efficacy of prophylactic nimodipine for delayed ischemic deficit after subarachnoid hemorrhage: a metaanalysis. *J Neurosurg* (1996) 84(3): 405–14. doi: 10. 3171/jns. 1996. 84. 3. 0405

PubMed Abstract | CrossRef Full Text | Google Scholar

23. Elliott JP, Newell DW, Lam DJ, Eskridge JM, Douville CM, Le Roux PD, et al. Comparison of balloon angioplasty and papaverine infusion for the treatment of vasospasm following aneurysmal subarachnoid hemorrhage. *J Neurosurg* (1998) 88(2): 277–84. doi: 10. 3171/jns. 1998. 88. 2. 0277

PubMed Abstract | CrossRef Full Text | Google Scholar

24. Marks MP, Steinberg GK, Lane B. Intraarterial papaverine for the treatment of vasospasm. *AJNR Am J Neuroradiol* (1993) 14(4): 822–6.

PubMed Abstract | Google Scholar

25. Rabinstein AA, Friedman JA, Nichols DA, Pichelmann MA, McClelland RL, Manno EM, et al. Predictors of outcome after endovascular treatment of cerebral vasospasm. *AJNR Am J Neuroradiol* (2004) 25(10): 1778–82.

PubMed Abstract | Google Scholar

26. Lad SP, Hegen H, Gupta G, Deisenhammer F, Steinberg GK. Proteomic biomarker discovery in cerebrospinal fluid for cerebral vasospasm following subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis* (2012) 21(1): 30–41. doi: 10. 1016/j. jstrokecerebrovasdis. 2010. 04. 004

PubMed Abstract | CrossRef Full Text | Google Scholar

27. Suzuki R, Masaoka H, Hirata Y, Marumo F, Isotani E, Hirakawa K. The role of endothelin-1 in the origin of cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg* (1992) 77(1): 96–100. doi: 10. 3171/jns. 1992. 77. 1. 0096

PubMed Abstract | CrossRef Full Text | Google Scholar

28. Ehrenreich H, Lange M, Near KA, Anneser F, Schoeller LA, Schmid R, et al. Long term monitoring of immunoreactive endothelin-1 and endothelin-3 in ventricular cerebrospinal fluid, plasma, and 24-h urine of patients with subarachnoid hemorrhage. *Res Exp Med (Berl)* (1992) 192(4): 257–68. doi: 10. 1007/BF02576282

PubMed Abstract | CrossRef Full Text | Google Scholar

29. Schoch B, Regel JP, Wichert M, Gasser T, Volbracht L, Stolke D. Analysis of intrathecal interleukin-6 as a potential predictive factor for vasospasm in subarachnoid hemorrhage. *Neurosurgery* (2007) 60(5): 828–36. doi: 10. 1227/01. NEU. 0000255440. 21495. 80

PubMed Abstract | CrossRef Full Text | Google Scholar

30. Zaroff JG, Leong J, Kim H, Young WL, Cullen SP, Rao VA, et al. Cardiovascular predictors of long-term outcomes after non-traumatic subarachnoid hemorrhage. *Neurocrit Care* (2012) 17(3): 374–81. doi: 10. 1007/s12028-011-9592-x

PubMed Abstract | CrossRef Full Text | Google Scholar

31. Zaroff JG, Rordorf GA, Newell JB, Ogilvy CS, Levinson JR. Cardiac outcome in patients with subarachnoid hemorrhage and electrocardiographic abnormalities. *Neurosurgery* (1999) 44(1): 34–9. doi: 10. 1097/00006123-199901000-00013

PubMed Abstract | CrossRef Full Text | Google Scholar

32. Zaroff JG, Rordorf GA, Ogilvy CS, Picard MH. Regional patterns of left ventricular systolic dysfunction after subarachnoid hemorrhage: evidence for neurally mediated cardiac injury. *J Am Soc Echocardiogr* (2000) 13(8): 774–9. doi: 10. 1067/mje. 2000. 105763

PubMed Abstract | CrossRef Full Text | Google Scholar

33. Zaroff JG, Pawlikowska L, Miss JC, Yarlagadda S, Ha C, Achrol A, et al. Adrenoceptor polymorphisms and the risk of cardiac injury and dysfunction after subarachnoid hemorrhage. *Stroke* (2006) 37(7): 1680–5. doi: 10. 1161/01. STR. 0000226461. 52423. dd

PubMed Abstract | CrossRef Full Text | Google Scholar

34. Naidech AM, Kreiter KT, Janjua N, Ostapkovich ND, Parra A, Commichau C, et al. Cardiac troponin elevation, cardiovascular morbidity, and outcome after subarachnoid hemorrhage. *Circulation* (2005) 112(18): 2851–6. doi: 10. 1161/CIRCULATIONAHA. 105. 533620

PubMed Abstract | CrossRef Full Text | Google Scholar

35. Lo BW, Fukuda H, Nishimura Y, Macdonald RL, Farrokhyar F, Thabane L, et al. Pathophysiologic mechanisms of brain-body associations in ruptured brain aneurysms: a systematic review. *Surg Neurol Int* (2015) 6: 136. doi: 10. 4103/2152-7806. 162677

PubMed Abstract | CrossRef Full Text | Google Scholar

36. Audibert G, Steinmann G, de Talance N, Laurens MH, Dao P, Baumann A, et al. Endocrine response after severe subarachnoid hemorrhage related to sodium and blood volume regulation. *Anesth Analg* (2009) 108(6): 1922–8. doi: 10. 1213/ane. 0b013e31819a85ae

PubMed Abstract | CrossRef Full Text | Google Scholar